

Amendments to the Specification

Please replace the Brief Description of the Drawings section, beginning on page 12 of the specification, with the following amended Brief Description of the Drawings section:

Brief Description of the Drawings

Figure 1 is a partial schematic diagram of a Ras pathway.

Figure 2A shows human (h) and mouse (m) CalDAG-GEFI, human (h) and rat (r) CalDAG-GEFII, and *C. elegans* (cel) (F25B3.3, GenBank accession number: 1262950) CalDAG-GEF.

Figure 2B shows a computer-generated phylogenetic tree analysis of the GEF domains of hCalDAG-GEFI and hCalDAG-GEFII in relation to mCdc25, hSos1, C3G, rRas-GRF, *C. elegans* (cel) (F25B3.3, GenBank accession number: 1262950) and BUD5.

Figure 2C shows multiple alignment of GEF structurally conserved regions (SCRs) of F25B3.3 (SEQ. ID NOS. 19, 20 and 21), hCalDAG-GEFI (SEQ. ID NO: 4: 150–173, ~~220–262~~ and 2998–320), hCalDAG-GEFII (SEQ. ID NO: ~~S: 63, 65 and 678: 205–229, 270–313, and 348–374~~), C3G (SEQ. ID NOS. 22, 23 and 24), mCdc25 (SEQ. ID NOS. 25, 26 and 27), rRas-GRF (SEQ. ID NOS. 28, 29 and 30), hSos1 (SEQ. ID NOS. 31, 32 and 33), BUD5 (SEQ. ID NOS. 34, 35 and 36) and *C. elegans* (cel) (F25B3.3, GenBank accession number: 1262950)(SEQ. ID NO: 37).

Figure 2D shows the full-length amino acid sequences of human (h) (SEQ. ID NO: 4), and mouse (m) (SEQ. ID NO: 2) CalDAG-GEFI (box indicates amino acid differences).

Figure 2E shows the sequence similarity (black indicates identity) of EF-hand domains in hCalDAG-GEFI (SEQ. ID NO: 4: 433–452), hCalDAG-GEFII (SEQ. ID NO: ~~860–427–447~~), hCalmodulin (SEQ. ID NO: 38), hCalbindin D28K (SEQ. ID NO: 39), hCalcineurin B (SEQ. ID NO: 40), hParvalbumin α (SEQ. ID NO: 41), hTroponin C (SEQ. ID NO: 42), and *C. elegans* (cel)(F25B3.3, GenBank accession number: 1262950 (SEQ. ID NO: 37)).

Figure 2F shows the sequence similarity of DAG-binding domains of hCalDAG-GEFI (SEQ. ID NO: 4: 499–548), hCalDAG-GEFII (SEQ. ID NO: ~~618–492–542~~), hPKC α (SEQ. ID NO: 44), hPKC β 1 (SEQ. ID NO: 45), hPKC γ (SEQ. ID NO: 46) and *C. elegans* (cel) (F25B3.3, GenBank accession number: 1262950)(SEQ. ID NO: 43).

Figure 3A is a schematic representation of human (h) cAMP-GEFI protein.

Figure 3B is a phylogenetic tree analysis of cAMP binding domains of cAMP-GEFI and II and other cyclic nucleotide binding proteins.

Figure 3C is a phylogenetic tree analysis of GEF domains of cAMP-GEFI and II and other Ras superfamily GEFs.

Figure 3D shows the amino acid sequences of the structurally conserved regions (SCRs) of human (h) cAMP-GEFI (SEQ. ID NO: 12: 616-639, 689~~8~~-731 and 768~~7~~-789), rat (r) cAMP-GEFI (SEQ. ID NO: 10: 61~~9~~~~8~~-642, 692~~1~~-734 and 771~~0~~-792), human (h) cAMP-GEFII (SEQ. ID NOS. 48 and 185~~9~~: 768~~7~~-791, 840~~3~~~~9~~-882 and 919~~8~~-940), rat (r) cAMP-GEFII (SEQ. ID NOS: 16: 192-216, 264-307 and 343-365~~6~~~~2~~, 64 and 66), celcAMP-GEF (SEQ. ID NO: 47, 49 and 50), hCalDEG-GEFI (SEQ. ID NO: 4: 150-173, 219-262 and 298-320), hCalDAG-GEFII (SEQ. ID NOS: 63, 65 and 678: 205-229, 270-313, and 348-371), C3G (SEQ. ID NOS. 22, 23 and 24), CDC25 (SEQ. ID NOS. 25, 26 and 27), rRas-GRF (SEQ. ID NOS. 28, 29 and 30), hSos1 (SEQ. ID NOS. 31, 32 and 33), and BUD5 (SEQ. ID NOS. 34, 35 and 36).

Figure 3E shows the amino acid sequences of the cAMP binding pockets of human (h) cAMP-GEFI (SEQ. ID NO: 12), and rat (r) cAMP-GEFI (SEQ. ID NO: 10), human (h) cAMP-GEFII (SEQ. ID NO: 59~~1~~~~8~~), celcAMP-GEF (SEQ. ID NO: 51), hPKAR1a A (SEQ. ID NO: 52), hPKAR1a B (SEQ. ID NO: 53), hPKAR1a B (SEQ. ID NO: 54), hPKAR1a B (SEQ. ID NO: 55), hPKG1a (SEQ. ID NO: 56), hPKG1b (SEQ. ID NO: 57), and hPKG1l (SEQ. ID NO: 58). The positions of invariant amino acid residues are shown by black diamonds. The open diamond indicates the amino acid that determines the binding specificity for cAMP or cGMP. The arrow indicates the position of amino acid substitutions specific to cAMP-GEFs.

Figure 3F is the full-length amino acid sequences of human cAMP-GEFI (SEQ. ID NO: 12) and human cAMP-GEFII (SEQ. ID NO: 59~~1~~~~8~~)(boxes indicate amino acid identity).

Please replace Table 1, on page 22 of the specification, with the following amended
Table 1:

TABLE 1

Gene	SCR1	SCR2	SCR3
hCalDAG-GEFI	SEQ ID NO.3: 6085-6797 SEQ ID NO.4: 15049-173	SEQ ID NO.3: 8187-946 SEQ ID NO.4: 22049-262	SEQ ID NO.3: 10553-112085 SEQ ID NO.4: 2998-320
hCalDAG-GEFII	SEQ ID NO.7: 70428-775800 SEQ ID NO.8: 2015-2249	SEQ ID NO.7: 9143-1042 SEQ ID NO.8: 2710-313	SEQ ID NO.7: 1151084-1216 SEQ ID NO.8: 35048-371
hcAMP-GEFI	SEQ ID NO.11: 206158-21320 SEQ ID NO.12: 616-639	SEQ ID NO.11: 228076-24085 SEQ ID NO.12: 6898-731	SEQ ID NO.11: 25176-2612582 SEQ ID NO.12: 7687-789
rcAMP-GEFI	SEQ ID NO.9: 20510-2122 SEQ ID NO.10: 6198-642	SEQ ID NO.9: 227067-2270396 SEQ ID NO.10: 6924-734	SEQ ID NO.9: 25072-257268 SEQ ID NO.10: 7710-792
hcAMP-GEFII	SEQ ID NO.17: 2222707-2293779 SEQ ID NO.18: 606767-629794		
rcAMP-GEFII	SEQ ID NO.15: 576144-648215 SEQ ID NO.16: 49248-71246		

Please replace Table 2, on page 23 of the specification, with the following amended Table 2:

Table 2

Gene	EF Hand Domain	DAG-Binding Domain
hCalDaG-GEFI	SEQ ID NO.3: 145 <u>76</u> -1516 SEQ ID NO.4: 433 <u>2</u> -452	SEQ ID NO.3: 1655 <u>2</u> -1804 SEQ ID NO.4: 4998 <u>5</u> -548
hCalDAG-GEFII	SEQ ID NO.7: 1532 <u>384</u> - 1591 <u>[444]</u> SEQ ID NO.8: 477 <u>27</u> - 496 <u>47</u>	SEQ ID NO.7: 1579 <u>1727</u> - 1875 <u>729</u> SEQ ID NO.8: 542 <u>492</u> - 591 <u>42</u>

Please replace Table 3, on page 23 of the specification, with the following amended Table 3:

Table 3

Gene	cAMP-Binding Domain
hcAMP-GEFI	SEQ ID NO.11: 2012 <u>906</u> - 2255 <u>1115</u> SEQ ID NO.12: 219 <u>231</u> -300
rcAMP-GEFI	SEQ ID NO.9: 887 <u>53</u> -1096 SEQ ID NO.10: 231 <u>19</u> -300
rhcAMP-GEFII	SEQ ID NO.17: 1522 <u>1070</u> - 1765 <u>1279</u> SEQ ID NO.18: 372 <u>222</u> - 291 <u>453</u>